BRIEF REPORT

# Brief Report of Anti–Programmed Cell Death Protein-1 in Human Immunodeficiency Virus Setting: Relevant and Breaking Results in First-Line NSCLC Therapy

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**ABSTRACT**

In the recent past, we observed an increased risk of cancer in the population with human immunodeficiency virus (HIV) owing to the development of antiretroviral therapies that decreased mortality caused by HIV-specific infections. This particularly fragile population is frequently excluded from clinical trials, and up-to-date recommendations for these patients are lacking. Only few cases of patients with HIV suffering from cancer and undergoing first-line immunotherapy have been reported so far. Here, we report the largest known study of patients with HIV with NSCLC (five patients) undergoing first-line immunotherapy by pembrolizumab, after CANCER-VIH group selection. Our results are consistent with those of previous case reports concerning safety of immunotherapy in patients with HIV, revealing no severe or fatal toxicity, opportunistic infections, or immune reconstitution inflammatory syndrome. Moreover, pembrolizumab did not seem to modify HIV viral parameters. We also evaluated the effectiveness of immunotherapy in these HIV-immunosuppressed patients: the average survival was 9.8 months, with three patients having rapid progression and two partial response. Nevertheless, besides safety and drug-to-drug interactions, the effectiveness of first-line immunotherapy in people living with HIV needs to be supported by larger studies.



*Keywords:* HIV; Anti–PD-1; $CD4^{+}$; Viral load; Lung cancer

## Introduction

The use of highly active antiretroviral therapy (HAART) in developed countries has led to considerable reduction in mortality from acquired immunodeficiency syndrome (AIDS) caused by opportunistic infections and

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AIDS-defining cancers. Instead, non–AIDS-related cancers have become a leading cause of morbidity and mortality in people living with human immunodeficiency virus (PLWHIV), with NSCLC being the first cause of mortality.[1] Because of a possible drug-to-drug interaction between chemotherapy and HAART, these patients require particular monitoring.

In the past 5 years, immune checkpoint inhibitors (ICIs)—notably programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors—have become the standard of care for advanced NSCLC in the general population, initially as second-line[2] and then as first-line treatment in patients with greater than or equal to 50% tumor PD-L1 expression[3] and finally in combination with chemotherapy in all patients, except those with oncogene-driven NSCLC. Because ICIs act by suppressing immune tolerance and reactivating an effective immune response, major concerns in PLWHIV were as follows: (1) a lack of antitumoral response owing to HIV-related chronic immune deficiency and (2) the risk of anti-HIV response modulation and deregulation of immune parameters, potentially leading to immune reconstitution inflammatory syndrome (IRIS).

Until recently, this population was rarely studied: only few cases in phase 1 and 2 clinical trials had described the use of ICIs as second or subsequent lines of treatment for PLWHIV with advanced NSCLC.[4] The CHIVA 2 trial has recently addressed the possible use of immunotherapy as second-line treatment for PLWHIV with advanced NSCLC[5]; however, safety and efficacy data on ICIs as first-line therapy are still lacking.

The French CANCERVIH network is a multidisciplinary task force supported by the French National Cancer Institute (INCa) whose mission is to optimize management and care of PLWHIV suffering from cancer. A main objective of CANCERVIH is to ensure equal care for PLWHIV, particularly through access to therapeutic innovations including immunotherapy.[6] Here, we report five cases taken from the CANCERVIH database of PLWHIV with advanced NSCLC and treated with first-line pembrolizumab.

## Methods

The CANCERVIH working group[7] has recommended that all new cases of PLWHIV with cancer should be included in the CANCERVIH database and discussed during the bimonthly national multidisciplinary board. Moreover, recommendations for immunovirological monitoring have been published.[8]

Between January 2014 and December 2019, a total of 105 PLWHIV suffering from lung cancer at various stages were presented. Among them, five with advanced NSCLC were eligible for first-line pembrolizumab monotherapy, having an Eastern Cooperative Oncology Group Performance Status less than or equal to 1, PD-L1 tumor expression greater than or equal to 50%, and patient agreement.

All patients received a fixed dose of 200 mg pembrolizumab every 3 weeks until disease progression or unacceptable toxicity. The outcome of this treatment is reported here (Table 1). The data for this analysis were collected from CANCERVIH database which one has received an approval from the French Institutional Review Board (no. 15-009), the CCTIR (no. 16-391), and the "Commission Nationale de l'Informatique et des Libertés (CNIL no. 916500)," and as a retrospective analysis, no consent is required.

## Results

The median age was 57.4 (range: 50–69) years, and four patients were men. Apart from one patient (case 3), all were current or former smokers. Tumor cell PD-L1 expression was 80% in two cases (cases 1 and 3). No epithelial growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations were found. All patients had undetectable plasma HIV load and were stable under antiretroviral treatment, except case 4, who had concomitant advanced NSCLC and HIV diagnostics (HIV load: 44,500 copies/mL). Median $CD4^+$ lymphocyte count was 595/$mm^3$ (range: 76–1024/$mm^3$). No opportunistic infection was reported.

At the cutoff date of data analysis (March 2020), median overall survival was 9.8 (range: 1–25) months and patients received a median of nine pembrolizumab infusions (range: 1–28) (Table 1). According to the Response Evaluation Criteria in Solid Tumors, best tumor response was partial response in two patients (40%) and disease progression in three patients (60%).

Two patients reported immune-related adverse events: grade 1 hyperthyroidism (case 2) and grade 3 immunologic thrombocytopenic purpura (case 4). None of the patients experienced IRIS, not even case 4, who received pembrolizumab concomitantly with HIV treatment by HAART.

HIV load remained or became (case 4) undetectable at cutoff, and blood $CD4^+$ lymphocyte counts remained stable in all patients.

## Discussion

Here, we report five cases of PLWHIV with advanced NSCLC treated with first-line pembrolizumab immunotherapy. No severe or fatal toxicity, opportunistic infections, or IRIS was reported during follow-up. Our safety results are consistent with those of retrospective series reported in the systematic review by Cook and Kim[4] (13 articles plus four reports from meetings including various types of cancers in PLWHIV receiving

**Table 1.** Outcome of Immune Checkpoint Inhibitor Therapy in PLWHIV With Advanced-Stage Cancers

| Source | Case # | PS | All NSCLC | Baseline $CD4^+$ Cells/$mm^3$ | Baseline VL (copies/mL) | Tumor PD-L1 (%) | ICI Start Date[a] (Infusions) | Best Tumor Response[b] | $CD4^+$ Cells/$mm^3$ at Cutoff[2] | VL at Cutoff[c] (copies/mL) | Survival (mo) | Status at Cutoff[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CANCERVIH | 1 | 2 | Adenocarcinoma | 413 | <30 | 80 | August 29, 2018 (5) | Progression | 319 | <30 | 9 | Death (May 2019) |
| CANCERVIH | 2 | 0 | Undifferentiated carcinoma | 1000 | <30 | 60 | August 8, 2019 (7) | Partial response | 342 | <30 | 8 | Alive (death on September 2020) |
| CANCERVIH | 3 | 0 | Squamous carcinoma | 463 | <30 | 80 | April 1, 2019 (1) | Progression | N/A | <30 | 3 | Death (July 2019) |
| CANCERVIH | 4 | 0 | Squamous carcinoma | 76 | 44,500 | ≥50 | February 13, 2018 (28) | Partial response | N/A | <30 | 25 | Alive |
| CANCERVIH | 5 | 1 | Undifferentiated carcinoma | 1024 | <30 | ≥50 | January 23, 2019 (4) | Progression | 1230 | <30 | 4 | Death (May 2019) |
| Source | N[d] | PS | Tumor Type | Baseline $CD4^+$ Cell Count | Baseline VL (copies/mL) | Tumor PD-L1 (%) | ICI Therapy (Treatment Line) | Best Tumor Response | $CD4^+$ Cells/$mm^3$ at Cutoff | VL at Cutoff | Overall Survival (mo) | Adverse Events |
| Uldrick et al., 2019[12] | 30 | 0-1 | Various advanced cancers (1 NSCLC) | 285 (132-966) | <200 | N/A | Pembrolizumab (second line) | 1 complete response (NSCLC) | Stable | Detectable (<400) in seven patients; stable in others | N/A | 80% grades 1-2: hypothyroidism (6/30 patients), pneumonitis (3/30), rash (1/30) |
| Gonzalez-Cao et al., 2020[13] | 20 | 0-1 | Various advanced cancers (14 NSCLC) | 397 (294-513) | Undetectable | <1: n = 11<br>1-49: n = 1<br>≥50: n = 3 | Durvalumab (all lines) | 25% partial response; 31% stable disease | Stable | Stable | 9.2 | Only grades 1-2 in 10/20 patients (diarrhea, asthenia, arthromyalgia) |
| Lavole et al., 2021[5] | 16 | 0-2 | Stages III-IV NSCLC | 385 (187-778) | 25 (0-44) | <1 or unknown: n = 11<br>1-49: n = 2<br>≥50: n = 3 | Nivolumab (≥second line) | 12.5% partial response; 50% stable disease | Stable | Stable | 10.9 | 69% grades 1-2; 1 patient with grade 3 pemphigoid |

[a]Pembrolizumab start date.
[b]Determined through investigator-assessed RECIST.
[c]Cutoff date was March 2020.
[d]Number of included patients.
#, number; ICI, immune checkpoint inhibitor; N/A, not applicable; PD-L1, programmed cell death 1 ligand; PLWHIV, people living with HIV; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; VL, viral load.

ipilimumab, pembrolizumab, nivolumab, or atezolizumab) and the observational study by Spano et al.,[9] which included 23 PLWHIV suffering from various malignancies (NSCLC [not including our cases], melanoma, head and neck cancers) and receiving pembrolizumab (first, second, or subsequent lines) or nivolumab (≥second line). This study reported only one case of grade 3 immune-related interstitial lung disease after pembrolizumab.

We also evaluated the effectiveness of ICI in these HIV-immunosuppressed patients and found an average survival of 9.8 months. Because of the small sample size, we cannot compare these data with larger studies in the general population.3 Three patients had rapid progression occurring only after one to five treatment cycles, despite the high PD-L1 tumor expression (>50%). In contrast, of two patients with partial response, one (case 2) had two additional cycles after data collection (nine in total) and then progressed and started chemotherapy (overall survival of 24 mo); the other had a longer-term response (case 4, 28 treatment cycles).

Nevertheless, high PD-L1 expression is only one prognostic factor of response to anti–PD-L1 immunotherapy and other potential markers are unknown. For example, one of our nonresponders (case 3) had 80% tumor PD-L1 expression but was also a nonsmoker, a condition which is unrelated to tumor immune response—even with high PD-L1 expression[10]—but rather relates to the activation of molecular pathways of addiction. Even if no EGFR or ALK mutations were found in this patient, many others were not evaluated. Alternatively, immunotherapy may be combined with chemotherapy in these patients, with a potential synergistic effect and improved response. Besides addiction pathways, another factor to be considered in PLWHIV is HIV-induced immune cell qualitative abnormality, which could potentiate cancer cell-mediated immunosuppression by means of PD-L1.

As for anti-HIV response, despite high expectations of anti–programmed cell death protein-1/anti–PD-L1 immunotherapy that followed in vitro studies revealing the reestablishment of anti-HIV immune response, recent in vivo observations did not support these results. Indeed, ICIs did not seem to modify viral parameters in stable PLWHIV or affect the response to HAART in newly discovered PLWHIV (case 4).[4,9]

Finally, our results are consistent with previous observations by Ostios-Garcia et al.[11] on three PLWHIV with advanced NSCLC receiving first-line pembrolizumab. Since this study, three more clinical trials[5,12,13] in PLWHIV have been published (Table 1). PLWHIV were also included in two additional phase 3 therapeutic trials, evaluating cemiplimab monotherapy as first-line treatment for advanced NSCLC with PD-L1 greater than 50%[14] and nivolumab in combination with low-dose ipilimumab versus platinum doublet chemotherapy.[15] Nevertheless, results for this group of patients have not been reported yet.

Indeed, we have to consider patients with HIV with uncontrolled infections separately, because all previous studies included patients with controlled immune response at baseline. Previous antiretroviral therapy is recommended in patients with HIV who have uncontrolled infections (as evidenced by high viral load and low $CD4^+$ cell counts), because the effectiveness of immunotherapy in these patients is unknown.

## Conclusions

We report 5 PLWHIV with NSCLC treated with first-line pembrolizumab immunotherapy. Besides safety and drug-to-drug interactions, the effectiveness of first-line immunotherapy in PLWHIV needs to be supported by large studies.

Inclusion of specific populations such as PLWHIV in clinical trials remains marginal, leading to considerable delays in drafting recommendations for these particularly at-risk patients.

## CRediT Authorship Contribution Statement

**Lise Bertin**: Investigation, Formal analysis, Writing.

**Armelle Lavolé:** Methodology, Member of the CANCERVIH group selecting patients, Writing, Supervision.

**Jacques Cadranel:** Member of the CANCERVIH group selecting patients, Supervision, Project administration.

**Anthony Canellas, Baptiste Abbar:** Member of the CANCERVIH group selecting patients.

**Marianne Veyri**: Methodology, Flow chart, Member of the CANCERVIH group selecting patients, Proofreading.

**Jean-Philippe Spano:** Member of the CANCERVIH group selecting patients, Proofreading.

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